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(54) Method and apparatus for improving blood sugar control in diabetics.

(57) The apparatus comprises an infusion means (2) and a control means (3) which controls the infusion rate of one or more diabetics control liquids. The control means comprises a basal rate means (4) to control infusion of the liquid according to an assessed basal metabolic requirement and a non-basal rate means (5) to control infusion of the liquid at one or more levels of metabolic activity. The control means is preferably adapted to receive patient data to vary the infusion of the liquid accordingly.
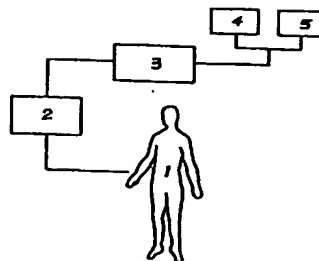
FIG. 1

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"METHOD AND APPARATUS FOR IMPROVING BLOOD
SUGAR CONTROL"

The present invention is directed to a method and
apparatus which will improve control of blood sugars in
5   diabetics.

At the present time there are two major problems
that face the insulin-dependent diabetic. Firstly there is
the problem of avoiding particularly high or particularly
low blood sugar levels which in themselves will cause
10   incapacity. In some diabetics, this is not too difficult,
but other "brittle" diabetics do have a considerable amount
of trouble avoiding hyperglycaemic or hypoglycaemic
(insulin) reactions. An "artificial pancreas" which would
maintain euglycaemic levels would be a great blessing for
15   diabetics, especially these brittle diabetics.

However, there is a far greater problem which
applies to all insulin-dependent diabetics. That is, the
problem of long term complications affecting the nerves,
blood vessels, heart, kidneys and eyes. There is much
20   evidence to suggest that if blood glucose levels could be
controlled in the ideal range by an artificial pancreas that
these worrying complications could be substantially reduced
or ameliorated.

Other recent developments have already made some
25   improvements in the life of the diabetic. Pure insulins
have abolished some of the reactions to insulin treatment,
particularly those of an allergic type. Measurement of
glycohaemoglobins (glucose altered haemoglobin) can now be
performed in many clinics and may give a better overall idea
30   of diabetic control than simple urine testing and occasional
blood glucose estimations. Frequent blood glucose
measurements performed at home by the diabetic have also
been a definite advance in helping the diabetic and his
physician know more about his blood sugar level, and thus
35   allow better adjustment of insulin dosage. However, none of
these developments represent a means by which the diabetic
can achieve "metabolic n rmality".

Two previous approaches to regulation of blood
glucose in diabetes as alternatives to insulin injections

have been proposed; pancreatic tissue implantation and apparatus that controls blood glucose concentration by means of feedback-control or preprogrammed insulin delivery. The mechanical devices can be divided into two categories:

5   closed-loop systems, in which insulin or other substances are given in response to a measured change in blood glucose, and open-looped systems, in which insulin is delivered in a preprogrammed manner independent of changes in blood glucose.

A closed-loop, insulin delivery system or a

10   pancreatic   cell simulator consists of three basic components: a glucose sensor, insulin or drug delivery pump and a controlling device that regulates the administration of insulin or other drug based on the measured amount of glucose. Ideally, such a system would be small enough to

15   offer the potential for implantation or prolonged-portable use. No such ideal device is currently available, primarily because neither glucose sensors nor insulin delivery pumps that are sufficiently small and reliable enough for long term use in vivo have been developed. Furthermore, even if

20   these two components were available, the problem of operating the controlling device to maintain blood glucose concentrations in ambulatory insulin-dependent diabetics within the narrow, physiological range seen in non-diabetics, still remains. The closed-loop artificial

25   pancreas basically responds to changes in blood glucose levels from minute to minute, analogous to the response of a healthy pancreas. However, the closed-loop systems have inherent problems. Early studies showed that a five to ten minute delay between blood withdrawal and glucose

30   measurement introduced an inherent delay in closed-loop control. This delay necessitated operation of the controlling device so that insulin administration was based on an extrapolated predicted glucose concentration. This prediction was a function of the actual glucose

35   concentration and its rate of change over the previous few minutes. Moreover, the necessity for a glucose sensor in the closed-loop systems inhibits the potential of these systems for miniaturization.

Open-looped insulin delivery systems attempt to

control blood glucose conc ntrations in diabetics whose
daily insulin requirements are predetermined during a
previous period of management. Basically, insulin is
infused so as to attempt to reproduce the pattern of diurnal
5   plasma insulin concentrations in a non-diabetic's plasma
before and after meals. Blood glucose is not measured but
instead the insulin infuser is directed to deliver insulin
to the diabetic according to preplanned instructions. A
fundamental problem arises in the production of a
10   commercially practical device, however, that different rates
of infusion are required for different anticipated basal
metabolic requirements and food ingestion levels of the
patient. Furthermore, since the actual levels may well
differ from the anticipated levels, some method of variation
15   of these rates will result in a better approximation to the
normal physiological response.

It is an object of the present invention to provide
an improved infusion system which overcomes, or
substantially ameliorates, the abovementioned disadvantages.
20   According to one aspect of the present invention,
there is disclosed an infusion system comprising an infusion
means and control means connected thereto to thereby control
the operation of said infusion means, said infusion means
comprising a first pump connected between a first diabetic
25   control liquid reservoir and a tissue access system
connected to the body of the patient whereby diabetic
control liquid from said reservoir is infused into said
body; and said control means comprising basal rate means to
operate said pump to a base rate corresponding to an
30   anticipated basal metabolic requirement of said patient, and
meal rate means to increase the operation of said pump by
predetermined amounts over a predetermined time
corresponding to anticipated ingestion of food by said
patient, both said basal rate means and said meal rate means
35   being adjustable to select one of a plurality of rates
corresponding to different anticipated levels of basal
metabolic requirements and food ingestion.

In a particularly preferred embodiment of the
present invention the system receives patient data at

predetermined intervals, preferably blood glucose levels, and the pump rate is varied responsive to said data. Preferably the blood glucose levels of the patient are entered into the control means at predetermined levels and

5 the control means assimilates this data and varies the pump rate accordingly. In this particular embodiment the hybridisation of the open loop system and the closed loop system allows more variable and adaptable control of blood sugar in diabetics.

10   Preferably, the present invention also includes means by which either insulin or dextrose or both, can be infused. In addition, the ability to adjust the basal and meal rates also permits adjustment according to the degree of insulin sensitivity of the patient (e.g. obese, child)

15 concerned.

In another preferred embodiment of the present invention, there is included means by which intravenous nutrition can be provided in the form of an infusible solution of dextrose, protein hydrolysates and other solutes.

20   Although the apparatus of the present invention finds a most useful application in the treatment of diabetes in man, the apparatus also lends itself to being a useful analytical tool to research the mechanism of such disorders, especially in conjunction with the glucose clamp technique,

25 which technique is described by DeFronzo, Ralph A., Jordan D. Tobin, and Reubin Andres, in "Glucose clamp technique: a method for quantifying insulin secretion and resistance." Am. J. Physiol. (237(3): E214-E223, 1979 or Am. J. Physiol.: Endocrinol. Metab.Gastrointest. Physiol.

30 6(3):E214-E223, 1979.

This technique is subdivided into two techniques: the hyperglycaemic clamp and euglycaemic clamp techniques which promise reproducible, physiological methods of quantifying cell sensitivity to glucose and tissue

35 sensitivity to insulin. In the first technique the plasma glucose concentration is maintained at an hyperglycaemic plateau by controlled infusion of dextrose first by infusion of a priming dose to raise the glucose levels in plasma and in extravascular glucose compartments to a predetermined

level, and secondly by maintenance doses at predetermined
intervals thereafter. The plasma insulin response is
monitored at the same time by blood sampling.

In the euglycaemic insulin clamp technique, a steady
5 state plateau of hyperinsulinemia is maintained by
controlled infusion of insulin. At the same time,
hypoglycaemia is prevented by application of the glucose
clamp technique, in order to maintain the subject at basal
plasma glucose levels.

10 The above techniques in conjunction with the
apparatus of the present invention provide a valuable tool
to study glucose homeostasis irregularities, by providing an
accurate and reliable means of controlling infusion of both
glucose and insulin to achieve predetermined plasma glucose
15 levels.

A preferred embodiment of the present invention will
be described by way of example only and with reference to
the accompanying drawings in which:

Fig. 1 is a block diagram of a basic open-loop
20 system;

Fig. 2 is a graph of the insulin infusion rate
against time for the meal profile used in the method and
apparatus of the present invention;

Fig. 3 is a block diagram of an infusion delivery
25 system for use with ambulatory patients;

Fig. 4 is a block diagram of an alternative control
device for an infusion system suitable for hospitalised
patients;

Fig. 5 is a schematic circuit diagram of the system
30 of Fig. 4; and

Fig. 6 is a graph of blood glucose as a function of
time which shows the improved control of blood glucose
possible in a "brittle" or "hard to control" patient using
continuous delivery of insulin subcutaneously in accordance
35 with the preferred embodiment.

Referring to Fig. 1, the open-loop system of the
preferred embodiment comprises an insulin infuser 2 which
supplies insulin to the patient 1. The rate of supply of
insulin is controlled by a control device 3 which operates

at either on of several base rates or one of several meal
rates according to whether basal rate selector 4 or meal
rate selector 5 is respectively selected.

5   The insulin infuser 2 of Fig. 1 comprises a pump
together with an insulin reservoir (not illustrated). The
pump is operated by a D.C. motor and gearbox which rotates
an eccentric cam to compress a tube connecting the reservoir
to the patient and thereby causing insulin to be delivered
to the patient 1.

10   The outlet of the pump is attached to a tissue
access system by which route the insulin and possibly in
addition, a suitable source of glucose, is administered.
The infuser 2 is capable of insulin delivery over a tenfold
range to provide a range of basal infusion rates and higher

15   rates for post prandial delivery. Post prandial insulin
delivery should be given in a time profile corresponding to
a normal metabolic post prandial response.

        Fig. 2 illustrates a preferred insulin infusion rate
which will simulate the normal pancreatic response to

20   ingestion of food, with a gradual return to the patient's
basal infusion rate over the post prandial period of 3 to 4
hours. The infuser 2 is designed to have selectable basal
infusion rates, preferably 3 rates, corresponding to normal,
reduced and enhanced basal rates, which substantially

25   respectively correspond to normal, reduced and enhanced
physical activity of the patient.

        The magnitude of these rates are predetermined from
a spread of possible magnitudes by, or under the direction
of, the patient's physician. The patient can then select

30   approximate basal rates for overnight, day-time, exercise,
etc., according to the patient's intended activity. A
preferred safety feature for ambulatory patients is a safety
device to prevent the patient (especially child patients)
altering the basal rate.

35   Precise post prandial infusion rates (or infusion
profiles) as a function of time for a particular patient
will be set in advance by the physician according to the
patient. Preferably, there is an optional facility of
selecting a reduced meal profile which will deliver a preset

smaller amount in insulin as an alternative to a normal meal
profile to cater for unexpectedly reduced amounts of food
intake.

There are three routes of insulin delivery through
5   the tissue access system, namely the intravenous route, the
subcutaneous route, and the intraperitoneal route.
Preferably, the route of delivery will be the intravenous
route, however, it will be clear to one skilled in the art
that the tissue access system can utilize any one of the
10 three possible routes.

There are of course special problems involved with
intravenous infusion. One such problem is the prevention of
entry or infection through the lumen of the catheter. This
problem is substantially avoided by incorporating into the
15 insulin and/or dextrose solutions one or more antimicrobial
agents, and/or by introducing the solutions into the insulin/
dextrose reservoir under aseptic conditions and/or
establishing a permanent seal at the junction of the
catheter and the pump outlet at the time of insertion of the
20 catheter.

Moreover, attention is paid to the dressing of the
skin wound at the point of insertion, and the catheter is
securely immobilized close to this point of insertion
through the skin. Strictly aseptic conditions are also
25 adhered to when inserting the catheter. For operation for
short periods of time i.e. less than 48 hours, a peripheral
vein is a convenient site of entry for the catheter.
However, for longer use, entry of the catheter to a cephalic
or cubital vein is generally necessary. Alternatively, and
30 preferably, a central vein such as the internal jugular,
external jugular and one of the subclavian veins is selected
for long term use.

Preferably, infusion rates of insulin and/or a
substrate source of glucose are tuned such that pulses at
35 intervals of less than 2 minutes are administered via the
intravenous route.

The subcutaneous route suffers from the disadvantage
of a delay in absorption of insulin. However, this route
can be used to successfully c ntrol basal and post prandial

hyperglycaemia provided sufficient allowance is made for the delay time in insulin reaction.

Irrespective of which route of insulin delivery is selected, the only part of the device to contact tissue will
5   be the catheter. The catheter can be made from silicon rubber, such as medical grade silicon rubber available from Dow-Corning of the U.S.A. Alternatively, heparinised polymer catheters can be used for the intravenous route since this material may provide an additional safeguard
10   against thrombogenesis.

The pump will vary according to whether the apparatus of the preferred embodiment is to be used with ambulatory patients, hence requiring a portable apparatus, or is to be used with hospitalised patients. For bedside
15   use preferably, two modified, servo-controlled peristalic pumps (manufactured by IVAC Corporation of the U.S.A.) are used. These pumps include sophisticated safety features and are well accepted in intensive care units. The abovementioned pumps are for use in bedside apparatus whilst
20   for ambulatory patients a smaller portable pump is used.

The insulin reservoir (not illustrated) of a portable system has a volume sufficient to maintain suitable dosages for patients up to seven days. One of the major problems with insulin is that its biological activity is
25   vulnerable at normal body temperature (i.e. $37^{\circ}C$) and this problem is a major barrier in the development of implantable devices. Hence, a reservoir with a supply of insulin lasting approximately 7 days is about the maximum volume able to maintain an active insulin supply.

30   Turning now to Fig. 3, a block diagram of one embodiment of the apparatus of the present invention, which is for use with ambulatory patients, is illustrated. The pump motor 30 is supplied with D.C. voltages derived from two sources. One of these sources is the basal rate
35   selector 4 which includes a switch able to be set at one of three positions so as to supply the pump motor 30 with one of three D.C. voltages. Accordingly, the basal rate selector 4 determines a base rate of rotation of the pump motor 30 and thus provides a base rate of insulin delivery

for the pump.

In order to supply a second source of D.C. voltage to the pump motor 30 and thereby result in the pump delivering at an increased rate corresponding to a meal

5 rate, the meal rate selector 5 is connected to a programmable read only memory 31 which, together with a clock 32, counter 33, and digital to analogue converter 34 comprises the control device 3 of Fig. 1.

The meal rate selector 5 includes a switch able to

10 be set at either one of two positions thereby resulting in the PROM 31 assuming either one of two corresponding memory states. The clock 32 drives the counter 33 at a predetermined rate through a single cycle of the counter 33 thereby causing the contents of the PROM 31 to be read to

15 the D to A converter 34. The D to A converter 34 converts the digital signal received from the PROM 31 into a D.C. voltage which changes as a function of time in accordance with the desired meal rate. This variable D.C. voltage when applied to the motor 30 increases the rate of operation of

20 pump so as to increase the amount of insulin delivered thereby. In this way, the delivery rate of insulin is increased beyond the basal rate in order to provide the meal rate for the duration of the cycle time of the counter 33.

Preferably, a pump speed detector 35, of any

25 convenient conventional construction, is also driven by the motor 30 so as to provide an indication of the rate of operation of the pump to an alarm 36. If the rate of operation of the pump falls below a first predetermined level, or rises above a second predetermined level, the

30 alarm 36 is actuated thereby advising the patient that too little, or too much, insulin is being delivered to him. The patient is then able to take the necessary corrective action, for example, by replacing the batteries (not illustrated) which supply the motor 30 and the remainder of

35 the circuitry, with electrical power.

As shown in Fig. 4, the bedside insulin delivery system consists of a micro computer 39 with associated peripheral inputs and outputs which correspond to th controller 3 of Fig. 1. The controller controls two pumps 2

and 46. One is the insulin infuser 2 of Fig. 2, whilst the
second is used for infusing dextrose. Switches, preferably
push-button switches, select different control programs
corresponding to the basal and/or meal selectors of Fig. 1.
5   Two additional control schedules are provided. These are
used if the patient becomes hypoglycaemic or hyperglycaemic.

In another preferred embodiment, not illustrated, an
additional control schedule is provided for intravenous
nutrition, by which additional or increased quantities of
10 dextrose can be infused, preferably in admixture with other
nutrients such as protein hydrolysates.

The appropriate control schedule is selected by
activating one of the basal 4, meal 5 hypoglycaemic 37, or
hyperglycaemic 38, rate selectors. These are used to select
15 different control schedules which are run on micro-computer
39. Blood glucose levels are entered using the blood
glucose entry sub-system 40. The level is dialled on
switches preferably thumbwheel switches, and a sample code
is entered. Preferably, a light emitting diode is activated
20 by the control schedules when a new blood glucose level is
required. Preferably, the bedside insulin delivery system
is adapted for better patient control by multiplying the
insulin pump rate by a "patient factor", which can be
entered so as to vary the insulin pump rate. Typically,
25 this is in the range of .5 to 3.0, preferably, 0.8 to 2.5,
and will vary, for example, with the obesity of the
patient. In a preferred embodiment of the invention, the
patient factor is entered by means of a thumbwheel switch 41.

The insulin 2, and dextrose 46 infusion pumps are
30 controlled by a pump interface 42. The pump rates are
loaded into a register in the interface 42 by the micro
computer 39. Preferably, the pumps are IVAC pumps and their
rate is determined by thumbwheel switches on the front panel
of the pumps. An insulin manual select 45 and a dextrose
35 manual select 48 can select the pump front panel rate as the
actual pump rate. A reset switch 49 over-rides this
selection and selects the prescheduled rate. It is
preferable that tw numeric displays 44 and 47 respectively
display the insulin and dextrose pump rates.

The data logging sub-system 50 is a printer with a
keyboard and a set of switches. The switches are used to
input the time of day to the system when it is switched on.
The keyboard is used to activate the data logging printout
5 on the printer. Preferably, the switches are thumbwheel
switches. Eleven different events activate the data logging
schedule. They are:

      1.   Start of basal rate
      2.   Start of meal rate
10   3.   Start of hypoglycaemic rate
      4.   Start of hyperglycaemic rate
      5.   Alarm signal from either the insulin or dextrose
          pump
      6.   Request for a blood glucose sample
15   7.   Activation of the manual rate on the insulin pump
      8.   Activation of the manual rate on the dextrose
          pump
      9.   Entering of a blood glucose level by an operator
     10. Hourly Status
20   11. Reset of alarm condition, reset of the manual
          operation of the pumps.

Typically, the data schedule records the time of
day, identifies the activating event, records the current
blood glucose level, the time the blood sample was taken for
25 the last blood glucose level, the number of drops of insulin
infused, the number of drops of dextrose infused and the
current patient factor. Upon request, this information is
output to the printer.

Preferably, an independent clock 51 is also provided.
30 Preferably, in the event of mains power failure, the
power supply 52 has a battery backup which allows the system
to run for approximately one hour. The power supply has
also circuitry to detect failure of the micro computer 39.
The pump interface 42 is monitored and if the pump rates are
35 not updated within a period of approximately one second,
then power is disconnected from the micro computer 39.

In use, the basal control schedule is started by the
basal rate selector switch 4. This sets a d fault value for
the insulin and dextrose infusion pumps 2 and 46, reads the

patient factor from the patient factor input switch 41 and requests the operator to enter via sub-system 40 a blood glucose level. Once the blood glucose level is entered, a pump rate is selected automatically from a look-up table

5 contained in the micro-computer 39 and multiplied by the patient factor. Typically, approximately every three hours a new blood glucose level is requested. The pump rates are set at default levels until a new value of blood glucose is entered.

10   The meal control schedule runs for approximately three hours and a look-up table contained in the micro-computer 39 contains the meal profile as shown in Fig. 3. Typically, about every two minutes a new pump rate is selected from the look-up table depending on the time. The

15 insulin pump rate is multiplied by the patient factor which is read when the schedule is selected.

         If the hypoglycaemic rate selector 37 is activated, an increased amount of dextrose is pumped to the patient for a predetermined period of time whilst the insulin rate is

20 decreased. Preferably, the dextrose pump rate increases to 75 drops per minute, and the insulin pump rate drops to 1 drop per minute for approximately 10 minutes only.

         If the hyperglycaemic rate selector 38 is activated, the insulin pump rate will be increased whilst the dextrose

25 pump rate is reduced. Preferably, the insulin pump rate is increased to about 48 drops per minute, whilst the dextrose pump rate drops to about 1 drop per minute for a predetermined time period of approximately 1 hour.

         When the meal, hypoglycaemic and hyperglycaemic

30 control schedule have expired, the basal control schedule is substituted.

         The circuit used to carry out the above functions is illustrated in Fig. 5 and comprises a micro-computer 101 to which various other integrated circuits are connected.

35   Contained within the micro-computer 101 are two peripheral interface adaptors each of which has 20 input/output lines made up from two 8 bit input/output p rts PA0-PA7, PB0-PB7 and four interrupt control lines CA1, CA2,

CB1 and CB2. Also contained within the micro-computer 101

is an erasable programmable r ad only memory (EPROM).

An internal two phase clock 02 is contained within the micro-computer 101 and the clock output is passed to a 14 bit binary counter 102 which produces an output having a

5 period of 14.187 seconds and which is applied as an input to the interrupt control line 1CA1. This arrangement functions to provide an internal time keeping arrangement with the micro-computer 101 which effectively enables it to ascertain the time of day and hence the elapsed time after a blood

10 glucose result has been entered or after the meal button has been pushed.

Two outputs 1PA0 and 1PA1 are connected to a 4 bit to 10 bit decoder 103 to which light emitting diodes (LED's) 130 to 133 are connected. These four LED's respectively

15 indicate whether the basal, meal, hypoglycaemic or hyperglycaemic rate schedules have been selected and are running. In addition, further outputs 1PA2 to 1PA5 are connected to a hex inverter 104 in order to activate selected ones of LED's 134 to 137 which respectively

20 indicate that a blood glucose sample is due to be obtained by the operator, and an alarm situation has arisen, that dextrose or glucose is being applied at a manual rate, and that insulin is being applied at a manual rate.

Furthermore the outputs 1PA4 and 1PA5 are each used

25 to blank four seven segment digital displays 115 to 118 and their respective segment display drivers 111 to 114 inclusive. In addition, the outputs 1PA4 and 1PA5 provide an automatic/manual control signal to the modified IVAC pumps which are respectively connected to pump sockets 151

30 and 152.

Data logging is achieved by means of an asynchronous communication interface adaptor (ACAI) contained within the micro-computer 101 and which permits a teletype machine to be controlled via transmit and receive lines TX and RX. The

35 signals from these lines are passed via two level converters 105 and 122 and thence to the socket 150 for the teletype machine. The level converters 105 and 122 convert the signal levels between that produced/required by the micro-computer 101 and that produced/required by the

teletype machine.

The pump rate for the insulin pump (not illustrated) connected to socket 151 is determined by quad latches 106 and 107 whilst the pump rate for the dextrose pump (not

5 illustrated) connected to socket 152 is determined by quad latches 108 and 109. The data for the latches 106 to 109 inclusive is provided from output lines 2PA0 to 2PA3 whilst the data is clocked into the latches 106 to 109 by output lines 2PA4 to 2PA7 respectively. The outputs from latches

10 106 and 107 are connected to the socket 151 for the insulin pump whilst the output of latches 108 to 109 is connected to the socket 152 for the dextrose pump. The logical complement of the output of latches 106 to 109 provides an input to the binary coded decimal to seven segment display

15 drivers 111 to 114 respectively. Thus the actual pump rates which are determined by the voltages applied to the pump sockets 151 and 152 respectively are displayed by means of displays 115 to 118 respectively. Displays 115 and 116 each display one digit of the two digit rate of the insulin pump

20 connected to socket 151 whilst displays 117 and 118 display one digit of the two digit rate of the dextrose pump connected to socket 152.

Eight push button switches 140 to 147 respectively are provided in order to initiate certain functions. Each

25 switch 140 to 147 is connected to a corresponding input 1PB0 to 1PB7 respectively and, via a pull-up resistor to a supply voltage and a corresponding input of an eight input NAND gate 123. The output of NAND gate 123 is applied to an interrupt input 1CA2.

30 The functions provided by the eight push button switches 140 to 147 are entry of glucose sample, manual delivery of insulin, manual delivery of dextrose, alarm, start of hypoglycaemic schedule, start of hyperglycaemic schedule, start of meal schedule and start of basal schedule

35 respectively.

Thus switch 140 is used to indicate t the micro-computer 101 that a new blood glucose level has been entered into thumbwheel switch 129 whilst the switches 141 and 142 are used to switch the insulin and dextrose pumps

from automatic to manual mode respectively. The switch 143 is used to clear the alarm display.

Operation of any one or more of th switches 140 to 147 enables the NAND gate 123 thereby providing the correct
5 signal for interrupt input 1CA2. Such an interrupt causes each of the inputs 1PB0 to 1PB7 to be scanned in turn to see which of the switches 140 to 147 generated the interrupt.

Furthermore, the pumps connected to sockets 151 and 152 cap generate an alarm signal and a pulse for each drop
10 of insulin or dextrose infused. These signals are applied to interrupt inputs 1CB1, 2CB1, 1CB2, and 2CB2 respectively. In this way the number of drops of both insulin and/or dextrose infused by the pumps is detected by the micro-computer 101 as is an alarm condition in respect of
15 either of the pumps.

Data is also input to the micro-computer 101 by means of the thumbwheel switch 129 previously described for entry of the sample blood glucose level, thumbwheel switch 128 for insertion of the patient factor and thumbwheel
20 switch 127 for insertion of time information.

A 4 bit to 10 bit decoder 110 driven by output lines 2PB4 to 2PB7 respectively selects each thumbwheel switch in turn and the value of each selected thumbwheel switch is read by the input lines 2PB0 to 2PB3 respectively.

25 It will be apparent that there are four control sequences which are activated by operation of switches 144 to 147 respectively. Operation of switch 147 starts the basal control schedule which sets a default value for the insulin and dextrose infusion pump rates, reads the patient
30 factor from the thumbwheel switch 128 and requests via LED 134, that the operator enter via switch 129 a blood glucose level. Once a blood glucose level is entered via switch 129 the micro-computer 101 uses it to select a pump rate from a look-up table and multiplies the pump rate by the patient
35 factor. Every two hours a new blood glucose level is requested. The pump rates are set at default (i.e. basal) levels until a new value of blood glucose is entered.

The m al schedule runs for three hours after activation of switch 146. A look-up table "contains" the

meal profile shown in Fig. 2 and every two minutes a new pump rate is selected from the look-up table depending on the time elapsed since activation of switch 146. The table pump rate is multiplied by the patient factor which is read

5   when the meal schedule is selected.

The hypoglycaemic control schedule is activated by switch 145 and sets the insulin pump rate to 48 drops/min. whilst the dextrose poump rate is set to 1 drop/min. This schedule runs for 1 hour.

10   At the end of the meal, hypglycaemic and hyperglycaemic control schedules, the basal control schedule starts running.

In addition there are two sub-schedules. The clock sub-schedule reads the initial value of the time from the 4

15   digit time thumbwheel switch 127. It then services the interrupts coming from input 1CA1 which are generated by the system clock. Thus the correct time is kept in the memory of the micro-computer 101.

The data logging sub-schedule is activated by one of

20   11 events. They are:

1.   Start of BASAL control schedule

2   Start of MEAL schedule

3.   Start of HYPOGLYCAEMIC control schedule

4.   Start of HYPERGLYCAEMIC control schedule

25   5.   Alarm signal from either of the insulin or dextrose pumps

6.   Request for a blood glucose sample

7.   Selecting the manual rate for the insulin pump

8.   Selecting the manual rate for the dextrose pump

30   9.   Entering a blood glucose level

10. Hourly status

11. Resetting of alarm condition.

The data recorded includes the time of day, identification of the event which initiated the data

35   logging, the current blood glucose level, the time the blood sample was taken, the number of drops of insulin infused, the number of drops f dextr se infused and the current patient factor. When the command P is typed on the teletype and thus entered via line Rx all the events recorded by the

data logging sub-schedule are printed. When an R is typed
the data logging sub-schedule is reset in order to restart
data logging so that memory overflow does not occur in the
micro-computer 101.

5   The details of the integrated circuits illustrated
in Fig. 5 are as follows:

PART NO.	MANUFACTURER	DEVICE NO.	DESCRIPTION
101	MOTOROLA	M68MM01A	Micro-computer
102	MOTOROLA	MC14020	14 Bit Counter
103	NATIONAL SEMICONDUCTOR	7441A	4 Bit - 10 Bit Decoder
104	NATIONAL SEMICONDUCTOR	7405	Hex Inverter
105	MOTOROLA	MC1488	Mos to RS232 Converter
106-109	MOTOROLA	MC14042	Quad Latch
110	NATIONAL SEMICONDUCTOR	7441A	4 Bit - 10 Bit Decoder
111-114	FAIRCHILD	9368	BCD to 7 Segment Display Driver
115-118	PLESSEY	GL8R04	7 Segment Display
112	MOTOROLA	MC1489	RS232 to Mos converter
123	NATIONAL SEMICONDUCTOR	74C30	8 I/P NAND gate

30   The following example illustrates the operation of
the apparatus of the preferred embodiment.

EXAMPLE 1

A preplanned meal program for the open loop delivery
system was tested. The schedule delivers 7.5 units of
35 insulin over 3 hours in a profile designed (by modelling
insulin kinetic data) to stimulate the normal meal insulin
response (peak incremental free insulin 78   16 mU/L). The
schedule has been implemented on both bedside and portable
insulin delivery systems. Six diabetics were studied for 48

hours on eight occasions; three were normal weight typical
insulin-dependent diabetics and three (two obese) were
commencing insulin after "tablet failure". For breakfast,
lunch and dinner, the peak blood glucose (BG) increments
were 2.0 0.7 (X SE), 1.4 0.7, 2.0 0.5 mmol/L and the
mean three hour post-prandial increments were 0.5 0.8,
0.6 5 and -0.3 1.0 mmol/L respectively. Exclusion of
the two obese subjects made little difference to the mean
values after meals although basal BG was higher in the obese
subjects (10.0 0.5 vs. 0.6 0.5 vs. 0.6 0.6 mmol/L).
The lunch BG increments were approximately 1 mmol/L less
(p 0.05) than those in six diabetics controlled with a
closed-loop system where BG changes determined insulin
delivery. This difference was attributed to prompt insulin
delivery with the open-loop system. The importance of early
initiation of insulin delivery for meals was confirmed in
three paired studies where a 15 minute delay in the meal
schedule resulted in higher one hour post-prandial BG level
in each subject (mean difference: 1.3 mmol/L). The results
demonstrate the practicability of a preplanned meal schedule
for control of post-prandial hyperglycaemia and stress the
importance of timing of insulin delivery with meals.

The foregoing describes only some embodiments of the
present invention and modifications, obvious to those
skilled in the art, can be made thereto without departing
from the scope of the present invention.

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<u>CLAIMS</u>

1.   An infusion system comprising an infusion means
and control means connected thereto thereby controlling the
operation of said infusion means, said infusion means
comprising a first pump connected between a first diabetic
control liquid reservoir and a tissue access system
connected to the body of a patient whereby diabetic control
liquid from said reservoir is infused into said body; and
said control means comprising basal rate means to operate
said pump at a base rate corresponding to an assessed basal
metabolic requirement of said patient, and meal rate means
to increase the operation of said pump by predetermined
amounts over a predetermined time corresponding to
anticipated ingestion of food by said patient, both said
basal rate means and said meal rate means being adjustable
to select one of a plurality of rates corresponding to basal
metabolic requirements of activity of food ingestion.

2.   A system as claimed in claim 1 wherein said
infusion means further comprises a second pump connected
between a second diabetic control liquid reservoir and said
tissue access system, said first and second reservoirs
containing insulin and dextrose respectively.

3.   A system as claimed in claim 2 wherein said
control means includes a hyperglycaemic rate means to
operate said first pump at a predetermined high rate and
operate said second pump at a zero or predetermined low rate
for a predetermined duration.

4.   A system as claimed in claim 2 or 3 wherein said
control means includes a hypoglycaemic rate means to operate
said pump at a zero or predetermined low rate for a
predetermined duration.

5.   A system as claimed in any one of the preceding
claims adapted to receive and store patient data relating to
the condition of said patient at predetermined intervals
whereby said control means varies said predetermined amounts
in response to said data.

6.   A system as claimed in claim 5 wherein said
patient data is blood glucose levels.

7.   A system as claimed in any one of the preceding

claims wherein said control means includes patient factor
means to vary said predetermined quantities in accordance
with the individual sensitivity of said patient to diabetic
control liquid(s).

8.   A system as claimed in any one of the preceding
claims wherein said control means includes a read only
memory storing value data at each of a plurality of
different locations, the data stored at each location
corresponding to the desired magnitude of a rate at a
predetermined time, timer means to read the contents of said
memory in a predetermined time, timer means to read the
contents of said memory in a predetermined sequence at each
predetermined time, and means to operate said pump(s) in
accordance with the read data values.

9.   A system as claimed in claim 8 when dependent
upon claim 7 wherein said patient factor means comprises
means to multiply said read data values with a selectable
one of a plurality of constants whereby said pump(s) are
operated in accordance with the numerical value of the
product of said selected constant and said read data values.

10.   An open loop infusion system substantially as
described with reference to Fig. 3 or Figs. 4 and 5 of the
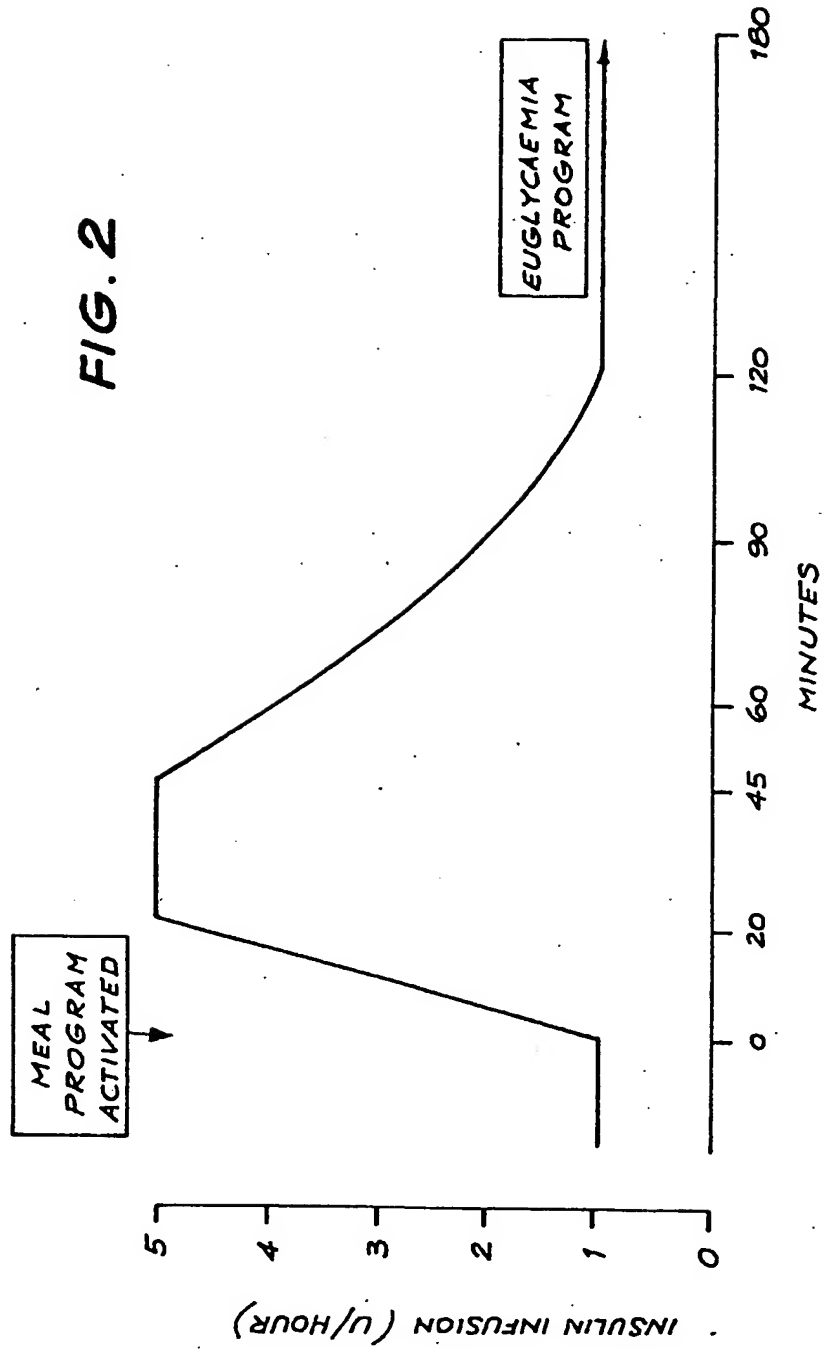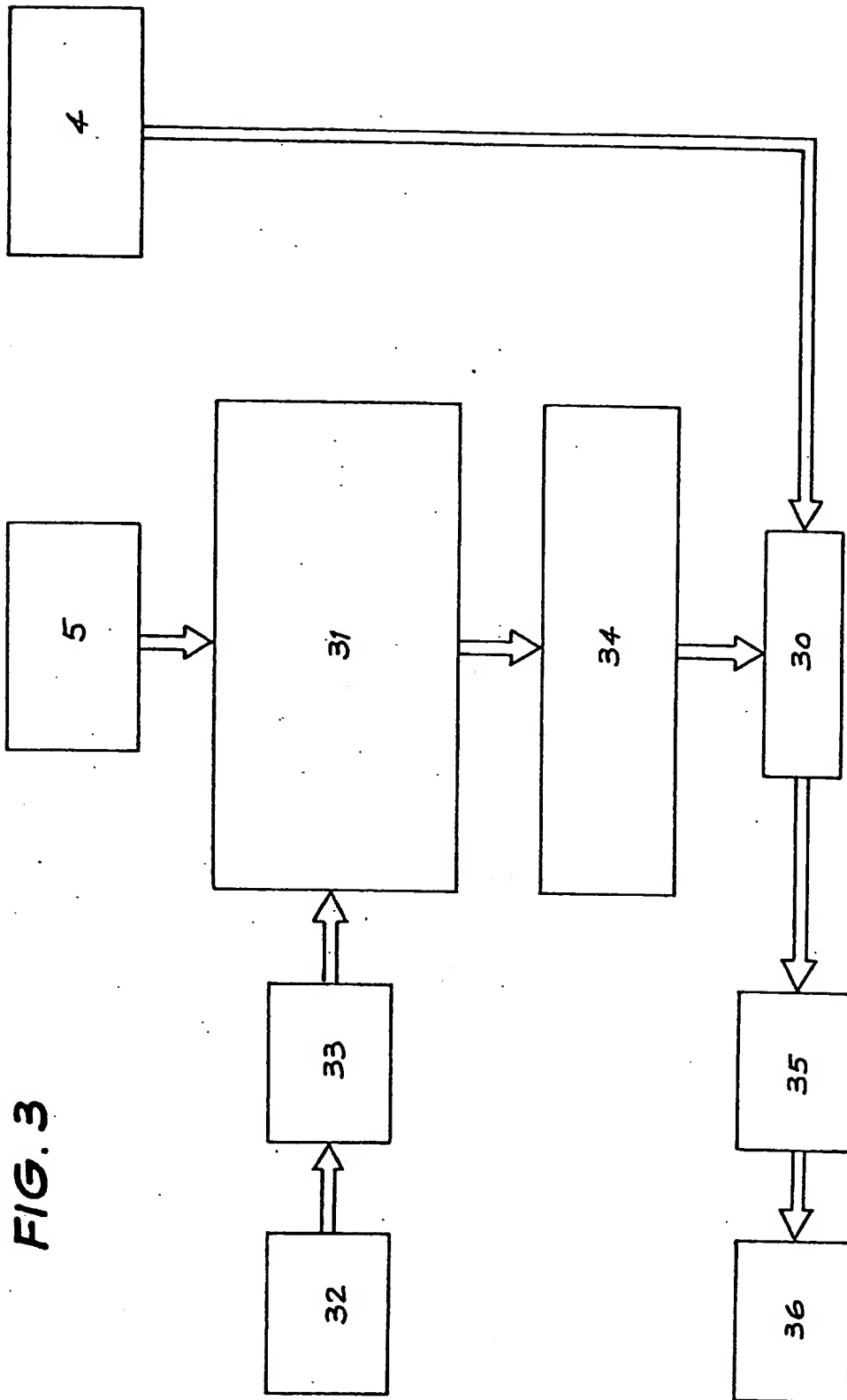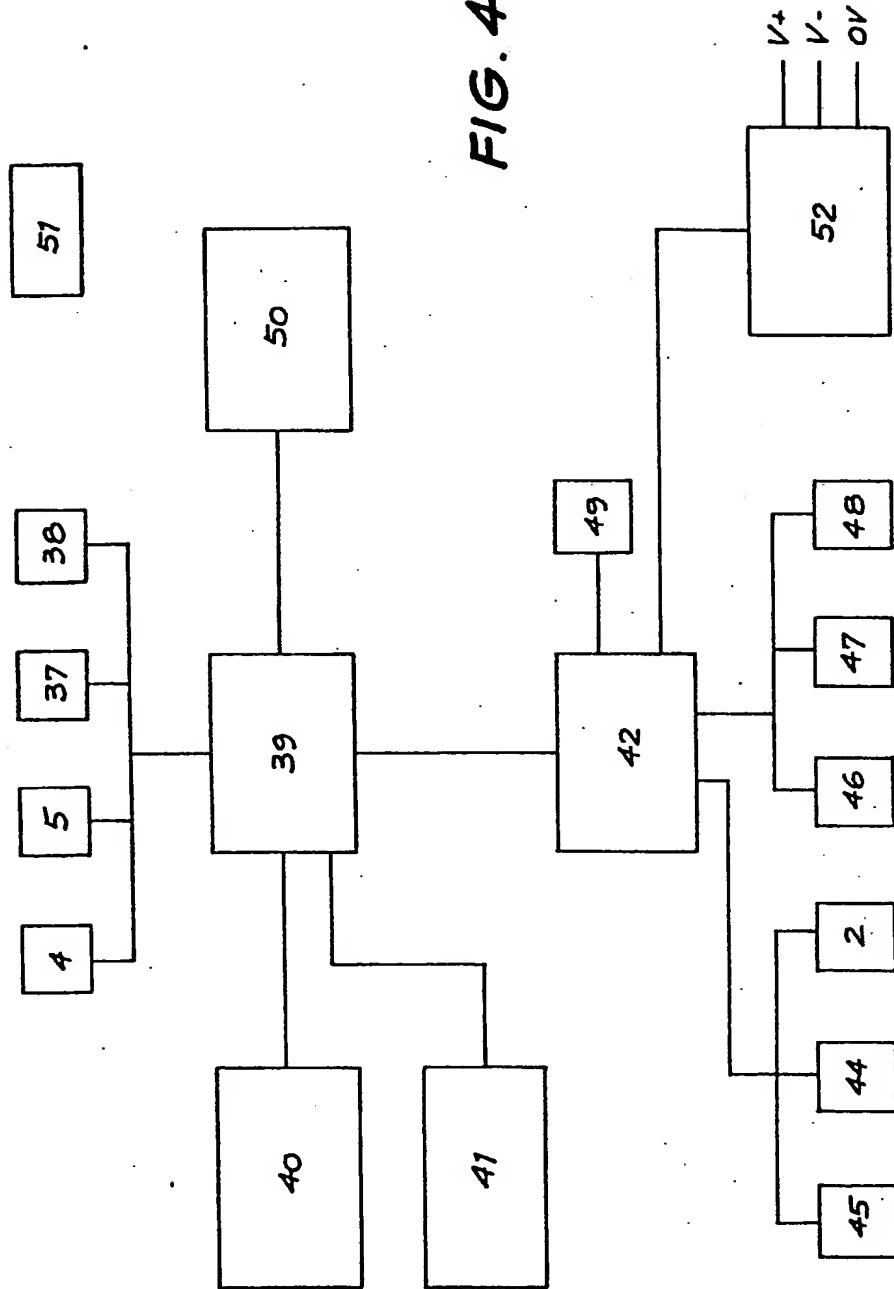drawings.

FIG.1

FIG.2

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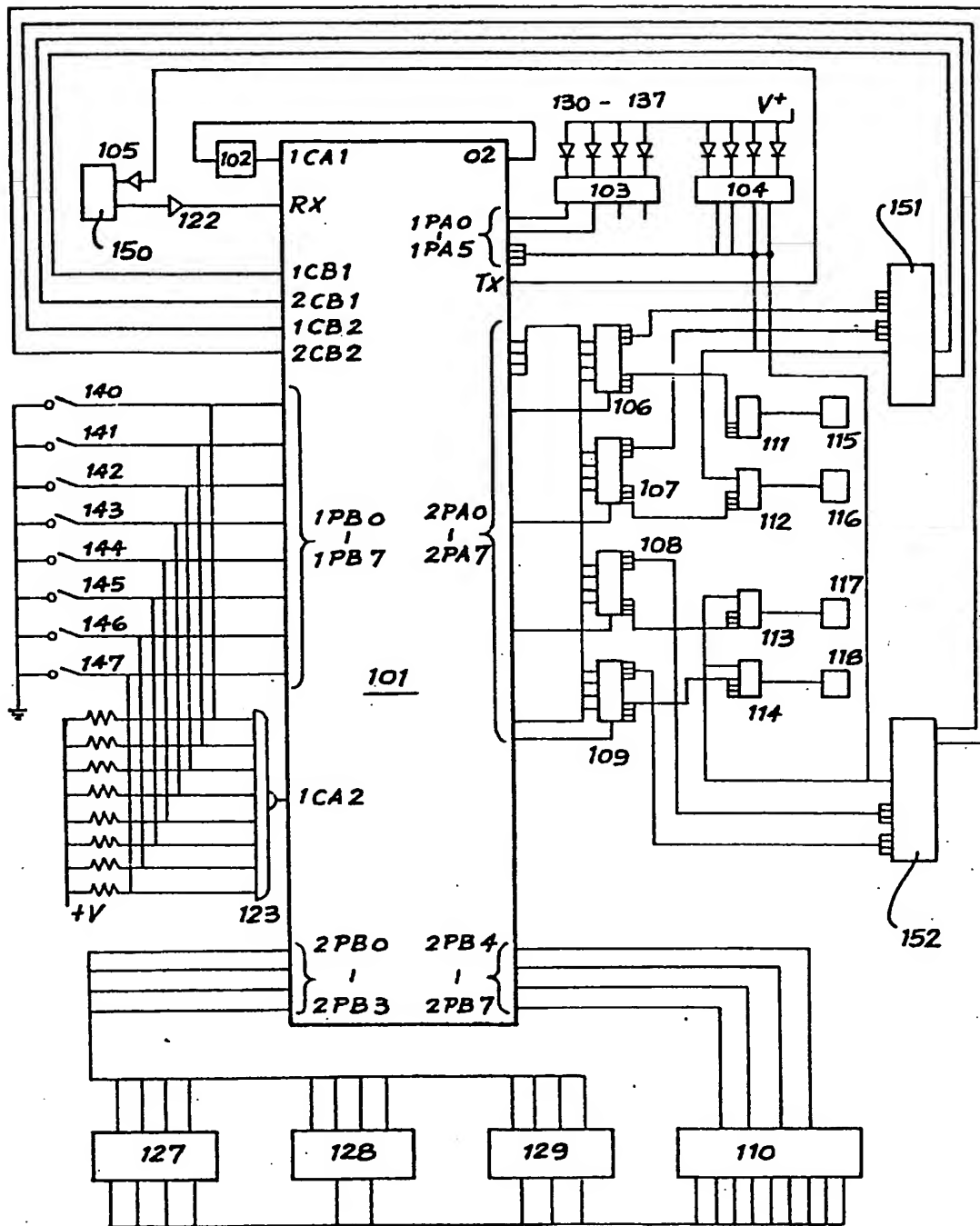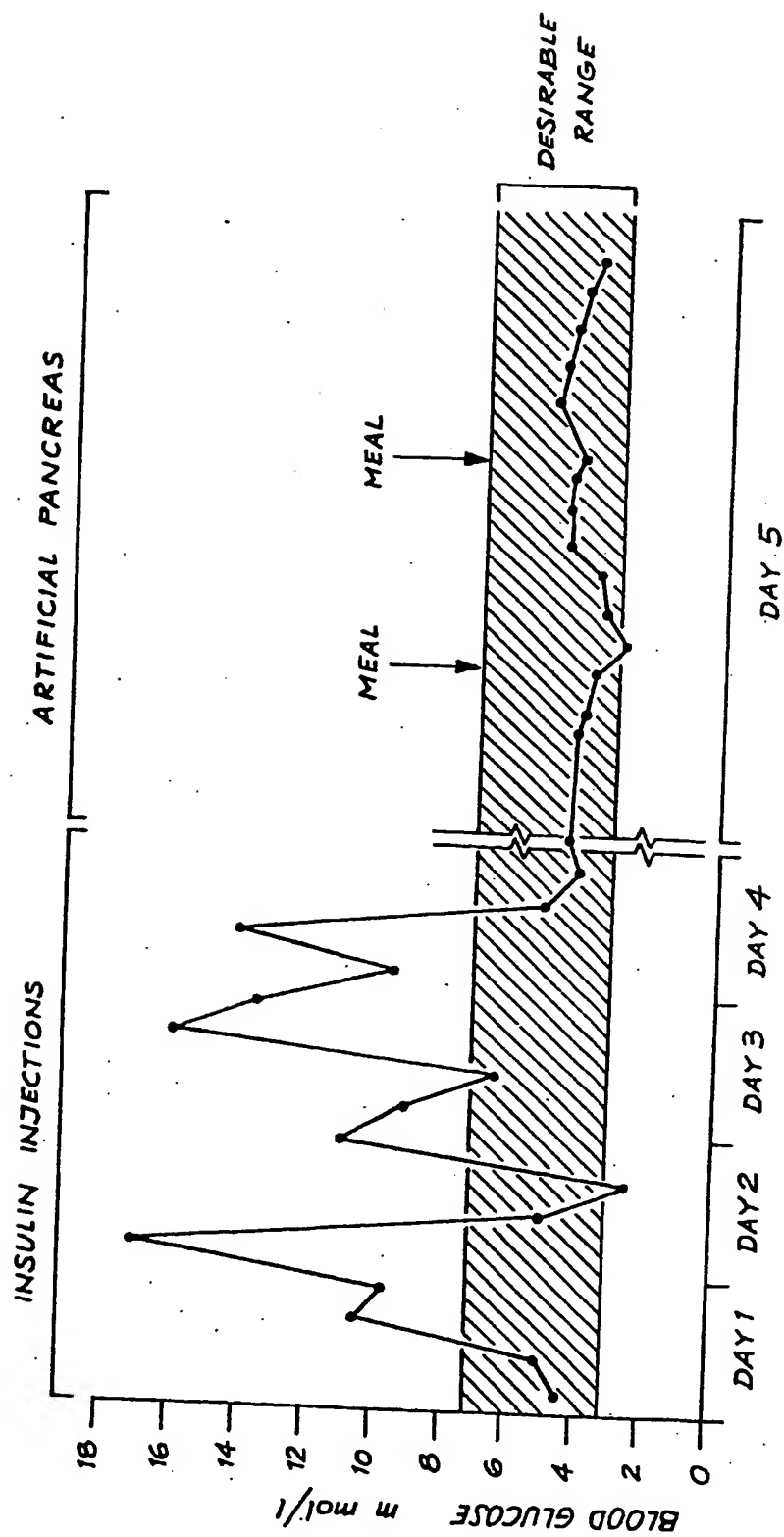
FIG.3
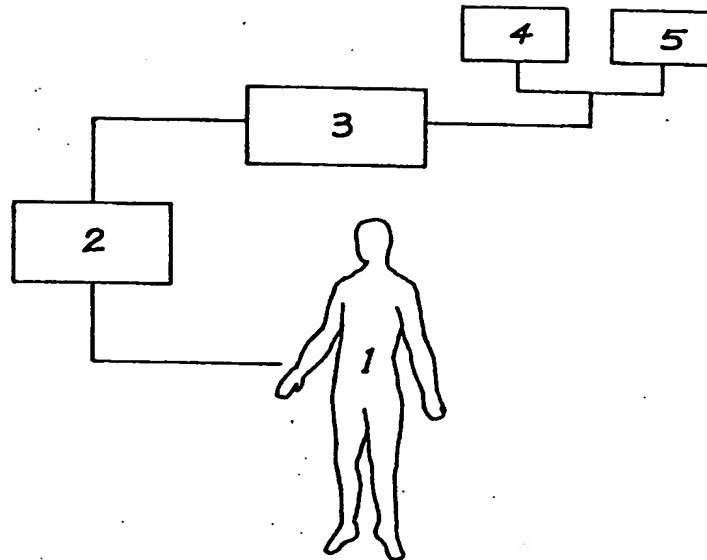
FIG. 4

FIG.5

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FIG. 6

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 81 30 5319

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
X	US-A-4 146 029 (ELLINWOOD) *Column 2, lines 35-46; column 5, lines 66-68; column 6, lines 1-20; column 7, lines 29-39; column 9, lines 14-60; figures 1,6,8,9*	1,2,3, 5,7	A 61 M 5/14

X	EP-A-0 039 124 (INFUSAID CORP.) *Claims 5,6; figures*	1	

A	US-A-4 078 562 (FRIEDMAN) *Claim 1; figure 1*	5	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 M
A 61 F

The present search report has been drawn up for all claims

Place of search THE HAGUE	Date of completion of the search 08-07-1982	Examiner VANRUNXT J.M.A.